Working with Center for Biologics Evaluation and Research

and

Suggestions for Successful Clinical Trials

Patricia Holobaugh

FDA Center for Biologics Evaluation and Research

Division of Inspections and Surveillance

Products Regulated by CBER

- Vaccines
- Toxoids for immunization
- Allergenic extracts
- Somatic cell therapies
- Gene therapies
- In vitro diagnostics
- Devices
- Whole blood
- Blood components
- Blood derivatives
- Antitoxins, antivenins, venoms
- Blood substitutes
- Tissues
- Xenotransplantation

Unique Challenges for Biologics

- Must be processed under defined conditions/controls throughout production to consistently produce a safe, pure, and potent product and preclude the introduction of environmental contamination
- Cannot withstand heat sterilization – must be aseptically processed

Vaccines
Toxoids for immunization
Allergenic extracts

- These products are administered to millions of healthy people, including infants
- Safety is paramount
  - Safety for recipient
  - Safety for household contacts

Vaccines
Toxoids for immunization
Allergenic extracts

- Starting materials may have inherent bioburden:
  - Egg-based vaccines
  - Starting materials may be infectious until inactivated (bacteria and viruses)
- From beginning to end, the process may take a year

Whole blood
Blood components
Blood derivatives
Antitoxins, antivenins, venoms

- For transfusion
- For manufacturing (example – clotting factors)
- CBER regulates cell separation devices and blood collection containers
- CBER establishes standards for these product
- FDA inspects blood establishments every two years, or more often if there are problems.

Somatic cell therapies
Gene therapies

Cell therapies are products composed of human or animal cells, or from physical parts of those cells.

Gene therapies introduce genetic material into the body to replace a defective or missing gene, or to treat or cure a disease medical condition.

Xenotransplantation

Xenotransplantation is any procedure that involves the transplantation, implantation, or infusion into a human recipient of either (a) live cells, tissues, or organs from a nonhuman animal source, or (b) human body fluids, cells, tissues or organs that have had ex vivo contact with live nonhuman animal cells, tissues or organs.

In vitro Diagnostics Devices

- Test kits used to screen donor blood, blood components and cellular products, and to diagnose, treat, and monitor persons with diseases (HIV, hepatitis, etc.)

- Devices used in collection, processing, testing, manufacture, and administration of licensed blood, blood components, and cellular components. Includes 510k blood establishment computer software.

Tissues

Requirements changed!

May 25, 2005 – new regulations went into effect for human cell, tissue, and cellular and tissue-based products (HCT/Ps).

New donor eligibility requirements in additions to 21 CFR Part 1271.

Current Good Tissue Practices - to prevent introduction, transmission, and spread of communicable diseases by HCT/Ps.

More establishments will be subject to FDA inspections.

~ 1900 registered establishments

FDA's Office of Combination Products

Determines which Center will have jurisdiction

- drug-device
  - *drug-eluting stent*
- device-biologic
  - *orthopedic implants with growth factors*
- drug-biologic
  - *monoclonal antibody-radionuclide*

CBER Reviews Many Types of Applications

BLA – Biologics License Applications

NDA – New Drug Applications

PMA – Premarket Approvals

510k

Sponsors should contact CBER's Office of Communications and Manufacturer's Assistance for help deciding which regulations apply

matt@cber.fda.gov 800-835-4709

Countering Bioterrorism

CBER plays an integral role under the President's Initiative on Countering Bioterrorism.

GOAL - Expeditious development and licensing of products to diagnose, treat, or prevent outbreaks from pathogens

Smallpox, anthrax, plague, botulism, tularemia, hemorrhagic fevers.

2004 Flu Vaccine – Lessons Learned

The Silver Lining

Last year's problems with the flu vaccine supply resulted in:

- A solid regulatory strategy to rapidly supply vaccine in case of an emergency
- Additional manufacturers seeking US approval
- Drawing of attention to importance of robust quality systems
- Highlighted the need to partner with our foreign regulatory counterparts

Meeting the Pandemic Flu Vaccine Challenge

- Increasing manufacturing diversity and capacity
- Developing needed pathways and regulatory processes to speed vaccine availability
  - Strain change, accelerated approvals on immunogenicity
- Assuring safety and public confidence
- Facilitating manufacturing and availability
- Considering pathways to prevent a pandemic
- Thinking and acting globally

Transfer of Products to CDER
June 30, 2003

Monoclonal antibodies for in vivo use, therapeutic cytokines and growth factors, and toxins for therapeutic indications

CBER continues to regulate these products when they are used solely as an ex vivo constituent in a manufacturing process or used solely as a reagent in the production of a product that is under CBER's jurisdiction.

CBER Regulation

Based on Sound Science, Law, and Public Health Impact

Surveillance of Product Safety

MedWatch

To report serious adverse events, product problems, or medication errors

- Voluntary for consumers and physicians
- Mandatory for drug/biologic manufacturers, distributors, and packers

Surveillance of Product Safety

Vaccine Adverse Event Reporting System (VAERS)

To report adverse events following vaccination.

- FDA and CDC
- Anyone can report to VAERS:
  - Health care providers, vaccine manufacturers, recipients or their parent/guardian, and state immunization programs.
  - www.vaers.org
- Not linked to Vaccine Injury Compensation Program

Surveillance of Product Safety

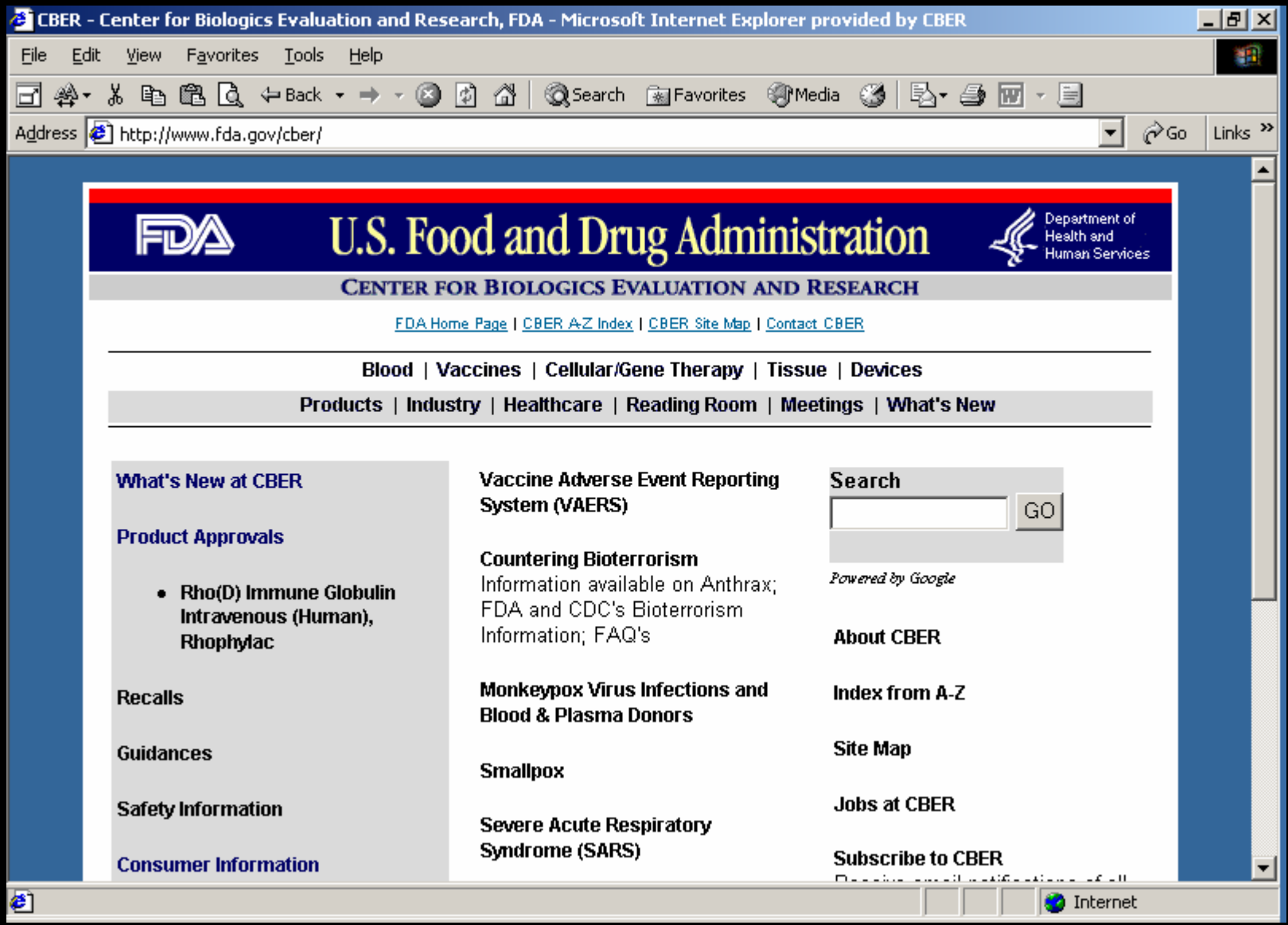
Biologic Product Deviation Reporting (BPD)

- Required for manufacturers of licensed biological products and for all manufacturers of blood and blood components.
- Must report errors and accidents that might affect safety, purity, or potency of a distributed product.
- Within 45 calendar days from date of discovery

Surveillance of Product Safety

Transfusion Related Fatalities and Donation Related Deaths

21 CFR 606.170 requires these to be reported. Initial notification may be by phone, fax, or email ASAP, followed by a written report within 7 days


CBER - Center for Biologics Evaluation and Research, FDA - Microsoft Internet Explorer provided by CBER
File Edit View Favorites Tools Help
Back Search Favorites Media
Address http://www.fda.gov/cber/
Go Links
FDA
U.S. Food and Drug Administration
Department of Health and Human Services
CENTER FOR BIOLOGICS EVALUATION AND RESEARCH
FDA Home Page | CBER A-Z Index | CBER Site Map | Contact CBER
Blood | Vaccines | Cellular/Gene Therapy | Tissue | Devices
Products | Industry | Healthcare | Reading Room | Meetings | What's New
What's New at CBER
Product Approvals
Rho(D) Immune Globulin Intravenous (Human), Rhophylac
Recalls
Guidances
Safety Information
Consumer Information
Vaccine Adverse Event Reporting System (VAERS)
Countering Bioterrorism
Information available on Anthrax; FDA and CDC's Bioterrorism Information; FAQ's
Monkeypox Virus Infections and Blood & Plasma Donors
Smallpox
Severe Acute Respiratory Syndrome (SARS)
Search
GO
Powered by Google
About CBER
Index from A-Z
Site Map
Jobs at CBER
Subscribe to CBER
Internet

CBER's Bioresearch Monitoring Branch

- Conduct pre-approval data audit inspections
- Investigate complaints
- Answer questions about Good Clinical Practices
- Help evaluate concerns about data integrity

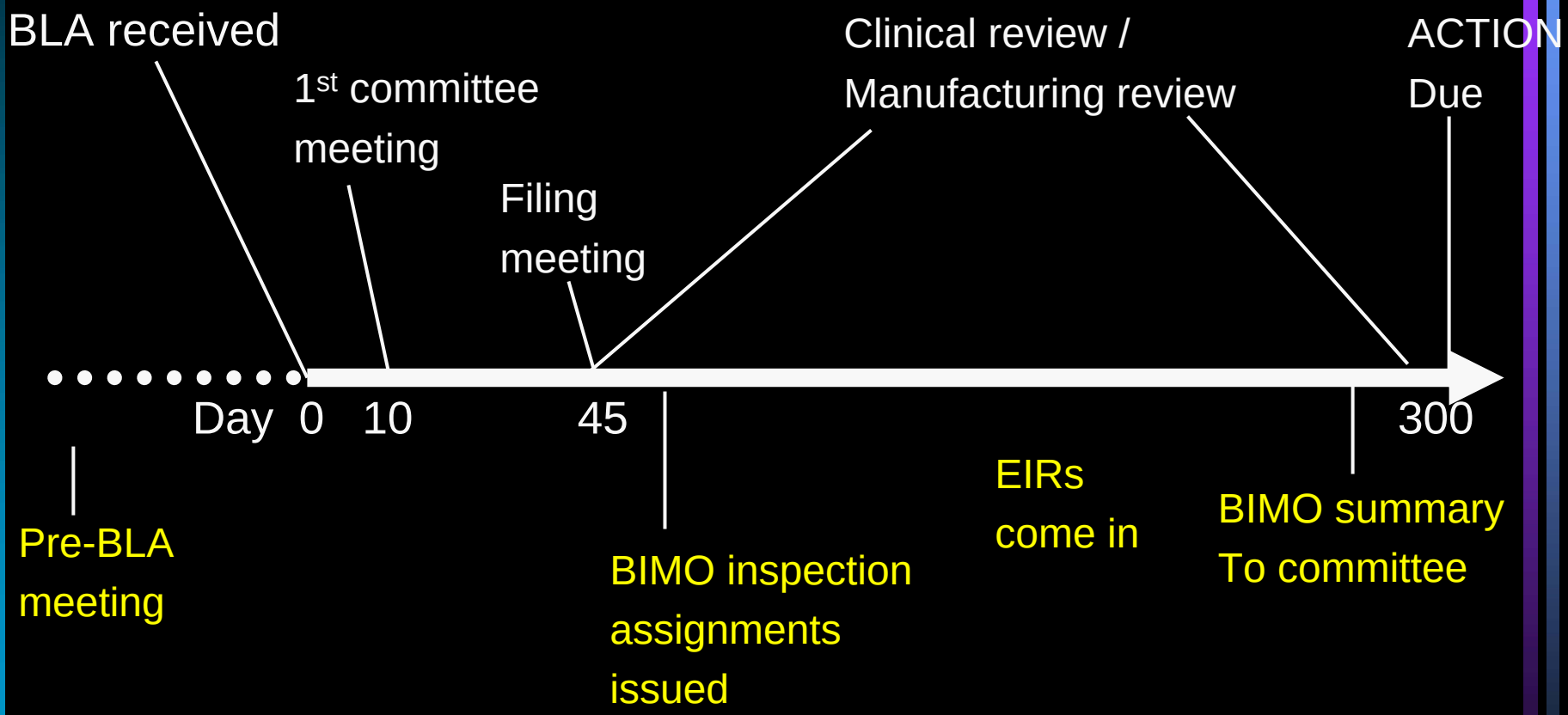
Clinical investigators

Sponsor/Monitor/CROs

IRBs

GLP/Nonclinical Labs

BIMO Milestones for Standard BLA



6-month Priority and PMA timeframes adjusted accordingly

CBER is assigning more inspections of ongoing studies under IND/IDE

"Real time" surveillance

- Cell therapies
- Gene transfer
- Vaccines
- Blood products
- Devices

For FY 2005, we inspected 50 sites enrolling pediatric subjects

True or False???

Clinical investigator: "I'm only doing phase 1 and 2 studies – I'll never be inspected by FDA."

True or False???

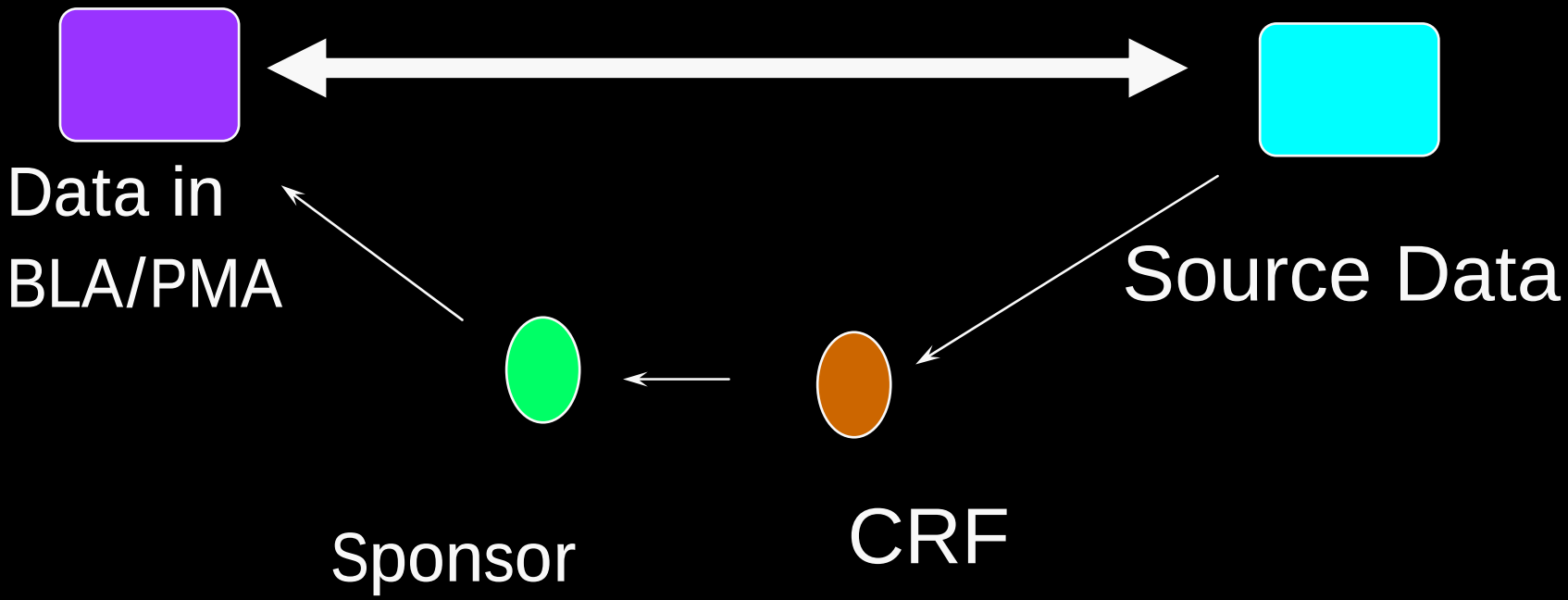
Clinical investigator: "I'm only doing phase 1 and 2 studies – I'll never be inspected by FDA."

FALSE

Clinical investigators of studies in all phases may (*and are*) inspected by FDA....

And ALL GCP regulations apply.

Comparison of Data in BLA / PMA to Source Data



CBER is expanding our inspections of clinical studies of blood *in vitro* diagnostics

Rapid kits to diagnose HIV, HBV, etc. in an individual

Diagnostic devices used to screen donated blood for blood supply

CBER is expanding our inspections of clinical studies of test kits

Preliminary findings:

- Higher rate of noncompliance by sites
- Lack of oversight by sponsors
- Lack of supervision by investigators
- Sponsors aren't checking on CRO activities

☹ Horror Stories ☹

Perform monitoring while critical activities are being performed.

We are hearing more reports of study staff lying about credentials and experience.

- ‘Nurse” with only high school degree
- Study coordinator fired from last 2 jobs for falsifying data

Are they now working with YOU???

Inappropriate delegation to subinvestigators

Investigator – individual who actually conducts an investigation (i.e., under whose immediate direction the drug is administered or dispensed to subjects.

**** How many miles (or states!) away ????

Sponsor must ensure that CI controls the study

***** BIG challenge for study coordinators and support staff

CBER Listing of Inspected Clinical Investigators is on Now On the Web !!

http://www.fda.gov/cber/compl/clininvlist.htm

Common Questions for FDA

Can case report forms be source documents?

Yes – protocol should specify how data are to be captured and records are to be maintained.

Are diaries, questionnaires, and photos subject to inspection?

Yes –these need to be maintained by investigator per 21 CFR 312.62(c)

Common Questions for FDA

Does FDA pre-audit systems & databases to ensure they are validated?

No - Sponsor is responsible for QA of computerized systems used by the sponsor, and for determining whether systems used by investigator sites are suitable for their study.

See FDA Guidance “Computerized Systems Used in Clinical Trials”

http://www.fda.gov/ora/compliance_ref/bimo/ffinalcct.htm

Suggestions to Prevent Noncompliance

- BEFORE -

- Understand what you are responsible for…

  …..And get training

- Document the delegation of duties

- Develop forms or checklists to make sure all screening tests and study visit activities are performed…*if not provided by the sponsor*

Suggestions to Prevent Noncompliance

- BEFORE -

- Develop a plan for organizing records
- Train study staff before the study starts….and train replacements when staff leave
- Don’t overextend to many concurrent projects

Suggestions to Prevent Noncompliance

- During -

- Track dates when reports are due to IRB and the sponsor
- Promptly report protocol violations to IRB and sponsor.
-
- Obtain written approval from the sponsor before you do something prohibited by the protocol

Suggestions to Prevent Noncompliance

- *During* -

- Verify that delegated duties are performed
- Work with monitors
- Correct small problems before they grow

Suggestions to Prevent Noncompliance

- *After* -

Organize the study records

- So non-study staff can find them
- To show what a good job you did
- To fulfill record retention requirements
- For possible FDA inspection

(years later - depending on the sponsor and phase of the research)

CBER is Here to Help You!!

www.fda.gov/cber

Email CBER :

Manufacturers: matt@cber.fda.gov

Consumers, health care professionals:

octma@cber.fda.gov

Phone: 800-835-4709 or 301-827-1800

CBER's Bioresearch Monitoring Branch

- Main phone 301-827-6221
- Branch Chief

  Pat Holobaugh 301-827-6347

  patricia.holobaugh@fda.hhs.gov
- FAX 301-827-6748